

# INTERNATIONAL COOPERATION TREATY

From the:  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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## WRITTEN OPINION

(PCT Rule 66)

Applicant's or agent's file reference  GM5084	Date of mailing (day/month/year)  06.03.2001	
International application No.  PCT/US00/12392	International filing date (day/month/year)  05/05/2000	Priority date (day/month/year)  07/05/1999
International Patent Classification (IPC) or both national classification and IPC  C12N15/12		
Applicant  THE GOVERNMENT OF THE UNITED STATES OF AM...et al.		

1. This written opinion is the first drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I     Basis of the opinion
- II     Priority
- III     Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV     Lack of unity of invention
- V     Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI     Certain document cited
- VII     Certain defects in the international application
- VIII     Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

**When?** See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

**How?** By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

**Also:** For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 07/09/2001.

Name and mailing address of the international preliminary examining authority:  
  
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Authorized officer / Examiner

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**I. Basis of the opinion**

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*):

**Description, pages:**

1-51                   as originally filed

**Claims, No.:**

1-39                   as originally filed

**Drawings, sheets:**

1/13-13/13           as originally filed

**Sequence listing part of the description, pages:**

1-2, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

## 4. The amendments have resulted in the cancellation of:

- the description,      pages:  
 the claims,      Nos.:  
 the drawings,      sheets:

5.  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

## 6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

## 1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

- the entire international application,  
 claims Nos. 23, 25, 27-31 (IA),

because:

- the said international application, or the said claims Nos. 23, 25, 27-31 (IA) relate to the following subject matter which does not require an international preliminary examination (*specify*):  
see separate sheet
- the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- no international search report has been established for the said claims Nos. .

## 2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- the written form has not been furnished or does not comply with the standard.  
 the computer readable form has not been furnished or does not comply with the standard.

**V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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**1. Statement**

Novelty (N) Claims 1-5, 8, 11, 12, 16-20, 23-37

Inventive step (IS) Claims 6, 9, 10, 13-15, 21, 22, 38, 39

Industrial applicability (IA) Claims

**2. Citations and explanations****see separate sheet**

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claims 25, 29, 30 and Claims 23, 27, 28 and 31, insofar as in vivo application is concerned, relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

For the assessment of the above claims on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**Re Item V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. The present application relates to viral vectors (retroviral, adenoviral) carrying genes encoding antiangiogenic proteins.  
Exemplified is an adenoviral vector comprising the endostatin gene.
2. Reference is made to the following documents:

- D1: WO 98 49321 A (LI HONG; LU HE; RAGOT THIERRY; YEH PATRICE;  
GRISCELLI FRANC; LEGRAND YV) 5 November 1998 (1998-11-05)  
D2: TANAKA T. ET AL.: 'VIRAL VECTOR-TARGETED ANTIANGIOGENIC  
GENE THERAPY UTILIZING AN ANGIOSTATIN COMPLEMENTARY DNA'

- CANCER RESEARCH, vol. 58, no. 15, 1 August 1998 (1998-08-01), pages 3362-3369, XP000857409 ISSN: 0008-5472
- D3: BRAMSON J. L. ET AL.: 'Direct intratumoral injection of an adenovirus expressing Interleukin-12 induces regression and long-lasting immunity that is associated with highly localized expression of Interleukin-12' HUMAN GENE THERAPY, vol. 7, 20 October 1996 (1996-10-20), pages 1995-2002, XP002093895 ISSN: 1043-0342
- D4: TANAKA T. ET AL.: 'Viral vector-mediated transduction of a modified platelet factor 4 cDNA inhibits angiogenesis and tumor growth.' NATURE MEDICINE, vol. 3, no. 4, 1997, pages 437-442, XP002145430 ISSN: 1078-8956
- D5: SCHWARZ M. ET AL.: 'EMAP II: A modulator of neovascularization in the developing lung.' AMERICAN JOURNAL OF PHYSIOLOGY, vol. 20, no. 2, February 1999 (1999-02), pages L365-L375, XP002145431 ISSN: 1081-5589
- D6: PIKE S. E. ET AL.: 'Vasostatin, a calreticulin fragment, inhibits angiogenesis and suppresses tumor growth.' JOURNAL OF EXPERIMENTAL MEDICINE, vol. 188, no. 12, 21 December 1998 (1998-12-21), pages 2349-2356, XP002145432 ISSN: 0022-1007
- D7: WO 97 34586 A (TSIARAS WILLIAM G ;SPEAR PETER D (US); BAETGE E EDWARD (US); CYTOT) 25 September 1997 (1997-09-25)
- D8: SHUTTLEWORTH C. A.: 'Type VIII collagen.' INTERNATIONAL JOURNAL OF BIOCHEMISTRY & CELL BIOLOGY, vol. 29, no. 10, October 1997 (1997-10), pages 1145-1148, XP000938722 ISSN: 1357-2725
- D9: RAMCHANDRAN R. ET AL.: 'Antiangiogenic activity of restin, NC10 domain of human collagen XV: Comparison to endostatin.' BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 255, no. 3, 24 February 1999 (1999-02-24), pages 735-739, XP002145434 ISSN: 0006-291X
- D10: RAMCHANDRAN R. ET AL.: 'Cloning, expression of a novel anti-angiogenic protein: Restatin.' PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, vol. 40, March 1999 (1999-03), page 620 XP000938553 ISSN: 0197-016X
- D11: BLEZINGER P. ET AL.: 'SYSTEMIC INHIBITION OF TUMOR GROWTH AND TUMOR METASTASES BY INTRAMUSCULAR ADMINISTRATION OF THE

ENDOSTATIN GENE' NATURE BIOTECHNOLOGY, vol. 17, no. 4, April 1999 (1999-04), pages 343-348, XP000857410 ISSN: 1087-0156 cited in the application

3. All of the documents D1 to D4 disclose viral vectors comprising antiangiogenic proteins.

In D1, for instance, a replication deficient adenovirus vector comprising a gene encoding an antiangiogenic factor (e.g. angiostatin, urokinase) is disclosed.

Further antiangiogenic proteins are mentioned to be useful in the invention (thrombospondin, endostatin). The vector is useful for inhibiting tumour growth. D1 is novelty-destroying for the subject-matter of Claims 1-5, 8, 11, 16-20 and 23-37.

Also D2 discloses viral-vector targeted antiangiogenic gene therapy by introducing angiostatin cDNA into a retroviral or adenoviral vector. It effects therefore the novelty of Claims 1-3, 8, 16-20 and 23-37.

D3 relates to adenoviral vectors comprising IL-12 for the treatment of tumours, thus destroying the novelty of Claims 1, 2, 11, 16, 18 and 23-31, while D4 shows that viral vector mediated transduction of platelet factor 4 inhibits angiogenesis and tumour growth (Claims 1-3, 5, 8, 12, 16-20, 23-31 and 37).

Consequently, the subject-matter of Claims 1-5, 8, 11, 12, 16-20, 23-37 is not novel in view of the above documents (Art. 33(2) PCT).

D11 discloses the expression of angiogenic factors (endostatin) fused to a signal sequence. Said document is therefore novelty-destroying for Claim 37.

4. EAMP-II, vasostatin, vasculostatin, collagen VIII, the NC10 domain of collagen XV and restatin are known as antiangiogenic factors (see D5, D6, D7, D8 and D9 and D10). To employ any of these for in a viral vector according to e.g. D1 would be obvious to the skilled person and does not require inventive skills. The subject-matter of Claims 6, 9, 10, 13, 14 and 15 does therefore not involve the required inventive step (Art. 33(3) PCT).

The use of an adenoviral signal sequence is not disclosed in the prior art. There

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SEPARATE SHEET**

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is, however, no indication in the description, that the use of the specifically claimed signal sequence brings about any unpredictable advantages in comparison to other signal sequences which were used in the cited prior art. Unless the applicant can show that selection of the particular signal sequence of Claims 21, 22, 38 and 39 is associated with a specific technical effect, no inventive step can be acknowledged for the subject-matter of said claims.

*The applicant is invited to file amended claims which take account of the above comments.*

*Any information the applicant may wish to submit concerning the subject-matter of the invention, for example further details of its advantages or of the problem it solves, and for which there is no basis in the application as filed, should be confined to the letter of reply and not be incorporated into the application (Article 34(2)(b) PCT).*

*In order to facilitate the examination of the conformity of the amended application with the requirements of Article 34(2)(b) PCT, the applicant is requested to clearly identify the amendments carried out, no matter whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based (see also Rule 66.8(a) PCT).*

*If the applicant regards it as appropriate these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed.*